REMARKS

Claims 1-3, 5, 9-33, 36-38, 41-44, 63 and 65-74 are indicated as pending in the application, with claims 1, 63, 65, 67 and 71 being independent and claims 11, 16-32, 63, 65 and 66 being withdrawn.

In the Final Office Action the Examiner construes claim 11 as (a) requiring the block copolymer to be bound to surface-modifying substances and thus (b) being withdrawn from further consideration as drawn to a non-elected species; however the Examiner indicates that claim 11 will be rejoined when parent claim 1 becomes allowable. Applicants thank the Examiner for so indicating.

Applicants also gratefully note that the rejection of claims 1-3, 5, 11, 14, 15 and 33 as allegedly anticipated under 35 USC 102(e) by Hirosue et al. (US 6254890) is withdrawn.

I. Amendment to the Specification

The Examiner requires that the reference to NH2-PEG-PLA synthesis being conducted in accordance with Kricheldorf and Pennings be deleted. Accordingly, the Specification has been so amended.

II. Rejection pursuant to 35 USC 112

Claims 1-3, 5, 9, 10, 12-15, 33, 36-38, 41-44 and 67-72 are rejected as being allegedly indefinite for the requirement in claims 1 and 71 that d) is able to attach to the polymer in an instant reaction. The Examiner states that no reaction is instant. Applicants respectfully traverse this rejection for the following reasons.

The Manual of Patent Examining Procedure (MPEP) states in § 2173.02 that the Examiner should allow claims which define the patentable subject matter with a reasonable

degree of particularity and distinctness. The essential inquiry pertaining to this requirement (of definiteness) is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. **Definiteness of claim language must be analyzed, not in a vacuum,** but in light of: (A) the content of the particular application disclosure; (B) the teachings of the prior art; and (C) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

The term "instant reaction" is elucidated on page 12, lines 21-25, which text corresponds to the sixth paragraph of the Specification. There, the Detailed Description indicates as "advantageous…the block copolymer or the shaped bodies formed therefrom [being] suitable for 'instant reactions' with the substance d), which means that they can be produced in advance as stock and stored without problem until application without having to be freshly prepared first for the scheduled application in a time-consuming manner" (emphasis added).

Additionally, on page 20, lines 14-20, the Specification describes "instant reactions" as follows:

> As a result of the simple type of binding of also unchanged, i.e. non-activated substances d), to the block copolymer with reactive group c) made possible according to the disclosure, the process can be simplified insofar as it is only necessary to dip the finished preshaped polymer carrier, e.g. in the form of micelles, nano-particles, polymer film or polymer sponge, into the solution of substance d) in order to then obtain the finished modified system after a predetermined reaction period (instant reaction).

Thus, the Specification contains ample, definitive, and explanatory content of the term "instant reaction" so as to denote clearly to any skilled artisan that "instant" is not of zero time duration. Consistent with the well-established axiom in patent law that a patentee or Applicant is free to be his or her own lexicographer, a patentee or Applicant may use terms in a manner consistent with, contrary to or inconsistent with one or more of their ordinary meanings if the written description

clearly defines the terms. *See*, e.g., *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999).

For these reasons, Applicants respectfully submit that the claims are not unpatentable for lack of definiteness, since the term is adequately defined and since no skilled artisan would interpret the common term "instant" as meaning a zero-duration (which is not chemically feasible in any context), and this rejection should therefore be withdrawn.

III. Rejections under 35 USC §103

A. *Obviousness "Problem to Be Solved" Analysis*

1. Small Number of Options

According to *Graham v. John Deere Co.*, 383 US 1, 148 USPQ 459 (1966), a patent claim is in violation of 35 USC §103(a) if the difference between the teachings of the prior art and of the claimed invention when taken as a whole are such that a person of ordinary skill in the art would find the claimed invention obvious in light of the prior art. In the recent United States Supreme Court case *KSR Int'l Co. v. Teleflex Inc.*, 550 US 398, 82 USPQ2d 1385 (2007), the Supreme Court stated that when there are "a finite number of identified, predictable solutions [to a given technical problem], a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 82 USPQ2d at 1396. The United States Court of Appeals for the Federal Circuit has recently clarified that the passage above in *KSR* posits a situation "with a finite, and in the context of the art, small or easily traversed, number of options that would convince an ordinarily skilled artisan of obviousness." *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 86 USPQ2d 1196, 1201 (Fed. Cir. 2008). Of course, the facts of both *KSR* and *Ortho-McNeil* disclose the existence of a "problem to be solved" that is amenable to a small, easily traversed number of options.

2. Large Number of Options

By contrast, the problem to be solved in the present case is not amenable to a small, easily traversed number of options. Prior to conception of the present invention, shaped block

copolymer bodies had not been formed/produced in advance as stock and stored without problem until application (i.e., "instant reaction" with the substance d)). Rather, such prior-art bodies required, following storage, fresh preparation for the scheduled application according to non-simple processes implemented in time-consuming manners.

The solution of the present invention focuses on providing a block co-polymer for the covalent binding of a surface modifying substance b) in an instant reaction with the substance b). Specification page 12, 2nd full paragraph. When articulated in terms of a problem to be solved by the present invention, it is immediately apparent that there exists a large set of known agents, combinations of such known agents, and possible new agents for the modification of an implant surface that may be particularly effective. It is also apparent that predicting *a priori* which of such agents may ultimately prove suitable for this purpose is difficult or impossible.

Chemical compositions also were at issue in the *Ortho-NcNeil* case. The court found that "the ordinarily skilled artisan would have to have some reason to select (among several unpredictable alternatives) the exact route" that provided the claimed composition. In finding the claimed compounds non-obvious, the *Ortho-McNeil* court concluded that, as in the present case, the prior art did not provide "the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness." *Ortho-McNeil,* 86 USPQ2d at 1201.

Even more recently, the United States Court of Appeals for the Federal Circuit has reaffirmed the non-obviousness principles expounded in *Ortho-McNeil*. In *Eisai Co., Ltd. v. Dr. Reddy's Laboratories, Ltd.,* 533 F.3d 1353, 87 USPQ2d 1452 (Fed. Cir. July 21, 2008), the patent at issue was directed to a proton pump inhibitor rabeprazole and its salts. Rabeprazole is related to other prior art proton pump inhibitors such as lansoprazole and omeprazole, differing solely by the nature of the group at the 4 position of the pyridine ring. Despite a very strong structural similarity between rabeprazole and prior art proton pump inhibitors, the Court of Appeals for the Federal Circuit found non-obviousness, again, limiting *KSR*'s obviousness

finding to situations where the record before the time of invention would support some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions."

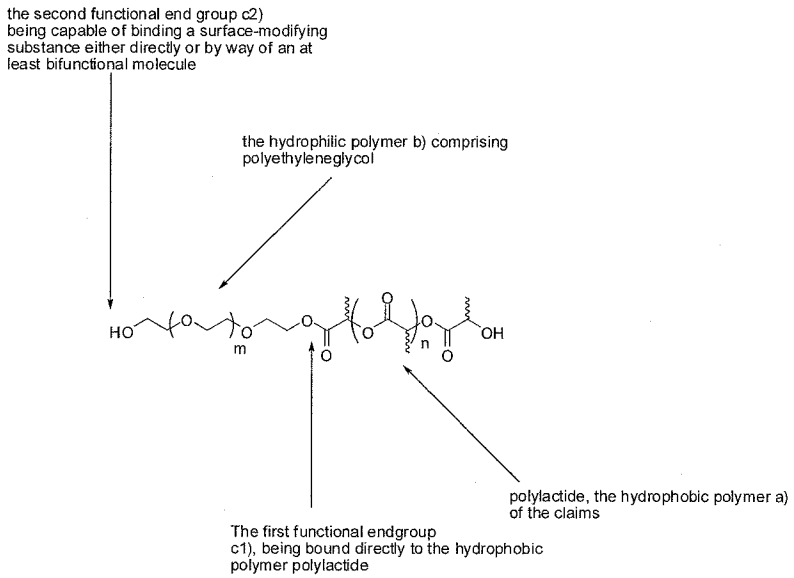
The *Eisai* court, referring to *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.,* 471 F.3d 1369, 1377, 81 USPQ2d 1324 (Fed. Cir. 2006) found that "[o]bviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e., a lead compound) in a particular way to achieve the claimed compound" (emphasis added). *Eisai* 87 USPQ2d. at 1455. Such motivation to make a particular compound or composition is especially necessary in the chemical arts because "[t]o the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable" (emphasis added). *Eisai*, 87 USPQ2d at 1457.

B. *Rejection of claims -3, 5, 9, 10, 12-15, 33, 36-38, 41-44 and 67-74 under 35 USC §103*

Claims -3, 5, 9, 10, 12-15, 33, 36-38, 41-44 and 67-74 are rejected as allegedly being obvious over Domb et al. (US 6365173, hereinafter "Domb") in view of Greenwald et al., BIOORG. & MED. CHEM. 6:551-562 (1998, hereinafter "Greenwald"). Applicants note that no claim number precedes the hyphen in the term "-3" and respectfully request clarification. For the purpose of this response only, the worst case (i.e., that "-3" encompasses claims 1-3) is assumed. Applicants respectfully traverse this rejection for the reasons provided above, and the additional reasons given below. Additionally, Applicants incorporate by reference, *mutatis mutandis*, the arguments made in response to the previous Office Actions regarding the Domb reference concerning non-obviousness.

In previous rejections Domb was cited for providing the molecular weights of PEG-PLA polymers. In the Final Office Action the Examiner for his characterization of Domb references a figure from the Office Action mailed September 4, 2008 (the "9/4/08 Office Action") and

interprets Domb as teaching use of this polymer "for binding to surface-modifying substances such as drugs and the like."



The 9/4/08 Office Action cited to column 6 and Example 11 of Domb as allegedly providing support for derivation of the above-shown structure. Column 6 of Domb lists various possible block co-polymers, including PLA-poly(ethylene and propylene oxides) Copolymers, and Example 11 describes the formation of Drug-PLA-PEG copolymer stereocomplexes employing L-PLA-b-PEG and D-PLA-b-PEG. The above figure, debuting on page 8 of the 9/4/08 Office Action as proposed by the Examiner, however, is nowhere disclosed in Domb. None of the formulae disclosed in Domb include the description in the figure legends appended by the Examiner, for example, none of the compounds of Domb is described as "capable of binding a surface-modifying substance either directly or by way of a bifunctional reagent."

This is because, contrary to allegations in the Office Actions, the polymers of Domb are not shown to form covalent bonds with any drug. Rather, Domb is drawn to polymeric carriers for drugs that are "complexed" with or "unincorporated on or with" the carrier. Domb, Abstract. As exemplified, the complexes are all formed by co-precipitation or solvent evaporation (*see, e.g.*, Examples 1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13); in certain cases the co-precipitation appears to be aided by hydrogen or ionic interactions, and/or followed by

melting or compression molding. In each case the co-precipitation/encapsulation appears to require at least a matter of many hours (Example 1, 24 hours or 3 days; Example 3, 24 hours; Examples 6 and 7, 3 days or one day; Example 8, 72 hours; Examples 9 and 10, 48 hours; Example 11, overnight; Examples 12, 13 and 14, 3 days).

Such complex formations are nothing like the "instant reaction" forming a covalent bond, as defined and claimed in the present application. Indeed, the Domb Abstract indicates that the bioactive compound may be complexed or the drug "bound to the complex by ionic, hydrogen or other non-covalent binding reactions not involving stereocomplexation," or "physically entrapped within the complex, either at the time of complex formation or when the polymeric material is formulated into particles, tablets, or other form for pharmaceutical application." There is no teaching or even suggestion in Domb that PLA-PEG copolymers are "used for binding to surface-modifying substances such as drugs and the like."

Thus, the statement at the top of page 4 of the Final Office Action that "[t]he difference between Domb and the claims is that the claims require a PEG with a terminal primary amine…whereas Domb teaches PEG with a terminal hydroxyl group" is misleading. Nothing in Domb suggests making the present copolymer capable of forming a covalent bond with a surface modifying substance in an instant reaction as defined and claimed according to the present invention.

The addition of Greenwald to the mix does not cure this deficiency. Greenwald is concerned with the conjugation of the chemotherapy drug camptothecin via an ester linkage and different linker groups to PEG in order to enhance the half-life, decrease toxicity, and enhance solubility of the unconjugated drug. *See* Greenwald at 551 and 552. The Final Office Action cites Scheme 1 of Greenwald as support for the attachment of a molecule to PEG using an amino PEG linker. However, this reaction, which combines compound 7 and compound 8 to form compound 10, is described to require reaction for 18 hours with stirring at room temperature, followed by removal of the solvent *in vacuo* and recrystalization from 2-propanol. *See* **PEG 40 kDa diamide of acid 7 (10);** Greenwald at 559, column 2. Clearly this compound is not

described in Greenwald as being capable of covalently binding d) in an "instant reaction," as described and claimed in the present application.

Furthermore, there is no reason why a person of ordinary skill in the art would be led to combine Domb and Greenwald, since they address completely different problems. Domb desires to form insoluble carriers which will slowly degrade to liberate an encapsulated drug. Greenwald is looking to form soluble prodrugs which can liberate the drug *in vivo* by utilizing endogenous esterases to hydrolyze an ester linkage, and does not disclose the use of a PLA-containing copolymer at all. *Id*. at 552.

Neither of these references, nor the combination of these references, discloses or suggests the presently claimed copolymer to the exclusion of any other possible copolymer.

For the reasons stated above, Applicants submit that the present invention would not have been obvious in view of the combination of Domb and Greenwald.

C. *Rejection of claims 1-3, 5, 9, 10, 12, 14, 15, 33, 36-38, 41-44 and 67-74 under 35 USC §103*

Claims 1-3, 5, 9, 10, 12, 14, 15, 33, 36-38, 41-44 and 67-74 are rejected as allegedly being obvious over Hirosue et al. (US 6254890, hereinafter "Hirosue") in view of Greenwald. Applicants respectfully traverse this rejection for the following reasons.

First of all, Applicants have previously argued that Hirosue, which is used as alleged prior art pursuant to 35 USC 102(e), is not actually prior art against any of the present claims pursuant to e.g., *Alexander Milburn Co. v. Davis-Bournonville Co.,* 270 US 390 (1926)(hereinafter *Milburn*), and *In re Wertheim and Mishkin*, 209 USPQ 554 (CCPA 1981)(hereinafter *Wertheim*). Contrary to the Examiner's position, neither of these cases has been reversed or overruled; however, even if Hirosue were prior art, Hirosue does not discuss or even suggest linear co-polymers containing a modified PEG, as are claimed in the pending claims.

The outstanding Final Office Action indicates that Hirosue discloses the same polymer as Domb, and refers the reader to the 9/4/08 Office Action. In that Office Action, the Examiner stated that Hirosue teaches the use of PEG-PLA and discusses functionalizing the PEG using N-hydroxysuccinimidyl esters so that amine groups from desirable ligands can be reacted with the copolymer.

Actually, although Hirosue discusses "activated esters (N-hydroxysuccinimidyl esters) on PEG-PLA," it does not discuss "functionalizing" PEG. Indeed, the mention of NHS is ambiguous; there is no clear indication where the NHS would be placed, e.g., on the PEG moiety or the PLA moeity. Further "activated ester on PEG-PLA" could be purchased without "functionalizing" PEG. Thus, despite the 9/4/08 Office Action's diagrams, there is no disclosure of a single compound (much less the depicted compound) that can be unambiguously and fairly derived from Hirosue.

Hirosue states "[t]he present invention discloses a biodegradable polymer nanosphere capable of 1) encapsulating nucleic acids, and 2) releasing nucleic acids over a period of time" (column 2, lines 20-22). In certain circumstances, Hirosue states, "masking moieties are attached to the surface of the nanospheres. These masking moieties prevent the recognition by a specific cell surface and instead allows for intravenous administration applications. For example, the surface masking characteristics are provided by poly(ethylene glycol) (PEG) by using various PEG-PLA and PLGA mixtures in the initial polymer solution. (Example 4)." Nanospheres can be made from PLGA, poly(e-caprolactone) and poly(hydroxybutyrate) and poly(orthoesters). As mentioned above, Example 4 states in full:

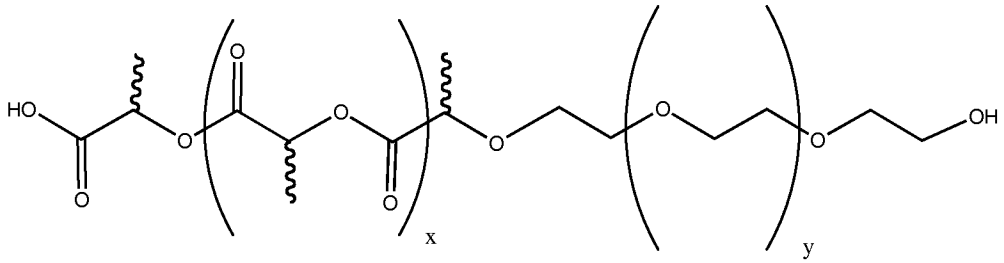
Method for Attaching Surface-Masking and/or Targeting Moieties

Surface masking characteristics are provided by PEG on the nanospheres by using various PEG-PLA and PLGA mixtures in the initial polymer solution.
Non-covalent attachment of targeting moieties is achieved by incubating

biotin-PEG-PLA: PLGA nanospheres with excess streptavidin or avidin, in turn, incubating the avidinylated spheres with biotin-ligand. **Covalent attachment methods use activated esters (N-hydroxysuccinimidyl esters) on PEG-PLA with which amine groups from desirable ligands can be reacted.**

The present invention does not contain activated esters, such as N-hydroxysuccinimidyl esters, on PEG-PLA.

Indeed, as argued in previous communications, Applicants completely reject the Office Action's premise that Hirosue discloses the molecule drawn by the Examiner on page 8 of the 9/4/08 Office Action. The only statement describing covalent attachment of molecules to the nanospheres of Hirosue is the sentence indicated in bold in the quote above. Even assuming arguendo that PEG-PLA can be unambiguously taken to refer to an A-B diblock structure, the structure shown below would be a far more feasible and likely structure to be envisioned by a person of ordinary skill in the art than the one proposed by the Examiner.



This is because to form an activated ester requires an ester linkage. Such a linkage is most easily and logically formed using a carboxylic acid group. A person of ordinary skill in the art, knowing that lactic acid is a carboxylic acid and can form PLA with a free carboxylate and be linked to PEG via an ether linkage, would far more likely understand Hirosue to be referring to this compound or another having a free caboxylate end than the one conjectured by the Examiner.

Moreover, the Examiner has alleged that it is common in the art to use the terminology PEG-PLA to refer only to linear, diblock co-polymers. However, as corroborated by evidence already made of record, PEG-PLA would have been understood by those skilled in the art to refer to tri-block and other co-polymer structures, as reflected, for instance, in Liggins et al., Characterization Of PEG-PLA Liquid Triblock Copolymers Useful For Controlled Delivery Of Paclitaxel (May 8, 2006) from the American Association of Pharmaceutical Scientists website (apparently a meeting poster presentation), which shows that "PEG-PLA" means ABA triblock co-polymers, rather than AB diblock co-polymers. *See* www.aapsj.org/abstracts/AM_2006/AAPS2006-002396.pdf. Thus, the term PEG-PLA is not unambiguous, and the disclosure of Hirosue simply fails to provide the required unambiguous description to render obvious any of the present claims, either alone or in combination with Greenwald.

The bottom of page 4 of the Final Office Action states that Hirosue "contemplates converting the hydroxyl group to an N-hydroxysuccinamide to facilitate reaction with other molecules such as d) of instant claims." The July 10, 2009 Office Action, in response to the fact that Hirosue does not actually reveal NH2-PEG-PLA, attempted to assert that Hirosue implicitly teaches amine terminated PEG because "[w]hen N-hydroxysuccinimide is attached to the terminus of PEG, it is by way of the nitrogen atom and the PEG terminus is in the form of an amine. Thus, Hirosue implicitly teaches amine terminated PEG." *See* July 10, 2009 Office Action, page 7, lines 2-4.

Respectfully, it does not. Even assuming arguendo the Examiner's basic linear, diblock structure to be correct, the Examiner is simply wrong that Hirosue's Example 4 disclosure that "**[c]ovalent attachment methods use activated esters (N-hydroxysuccinimidyl esters) on PEG-PLA with which amine groups from desirable ligands can be reacted"** implicitly teaches amine terminated PEG or yield the structure shown on page 8 of the 9/4/08 Office Action. This is because the reaction of a primary amine with an NHS ester results in an amide (not an amino) linkage rather than the secondary amino linkage shown in the Examiner's figure debuted on page 8 of the 9/4/08 Office Action.

As indicated in the response to the July 10, 2009 Office Action, the Examiner's argument quoted above is circular, in that it assumes, without any support in the cited prior art, that PEG is terminated with an amine; exactly the thing that it purports to prove. In other words, it begs the question by way of the proponent (the Examiner) assuming a controversial key point (that PEG is terminated with amine) not conceded by the opponent (the Applicants). The argument is *Circulus In Probando* by using the very fact sought to be proven as a premise, *i.e.* as part of the evidence on which the conclusion is based, and further is *Non Sequitur* as a consequence of its conclusion not logically flowing from its premise/presentation. Applicants respectfully ask the Examiner to point out the evidence in Hirosue disclosing the PEG terminus is in the form of an amine. Applicants note that PEG contains no nitrogen atom.

For these reasons, Applicants respectfully but strongly disagree with the characterization of the teachings of Hirosue.

The Examiner indicates on page 5 of the Final Office Action that "[i]t would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to substitute PEG-amine for PEG-hydroxysuccinamide in Choe." Applicants assume the Examiner meant to say "Hirosue" rather than "Choe."

As indicated above, Hirosue does not disclose amino-PEG. Furthermore, Greenwald is drawn to a method for drug delivery and a product/prodrug used in this method that requires the delivery of drugs linked to a carrier in vivo by way of a "readily hydrolyzable" ester bond. Greenwald at 551. As shown above, a person of skill in the art, seeking a solution to the problem of creating a co-polymer for use in an "instant reaction" (as this term is defined in the Specification) would not look to Greenwald, in which the attachment of a ligand to PEG requires reaction of all components in solution for 18 hours. Greenwald at 559, column 2, third paragraph.

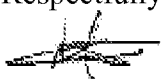
Thus, the combination of Hirosue with Greenwald, as the combination of Domb with Greenwald, does not render the present claimed invention obvious. Respectfully, it appears that the Examiner has used improper hindsight knowledge of and reference to the present application to find the invention obvious. While Applicants are aware that any obviousness inquiry must, to some degree, employ a permissible degree of hindsight, hindsight is always improper when, as here, the claimed invention is being used as a template for construction using the prior art to find the elements without any clear motivation or suggestion, and where the prior art does not provide "the easily traversed, small and finite number of alternatives [to solving the problem at hand] that *KSR* suggested might support an inference of obviousness." *Ortho-McNeil,* 86 USPQ2d at 1201.

IV. Conclusion

For the reasons presented, Applicants submit that the claims are in condition for allowance, and request reconsideration and withdrawal of the rejections under 35 USC §112 and 35 USC §103. The Examiner is requested to consider the application now to be in condition for allowance, and an early indication of same is requested. Of course, Examiner Silverman is welcome to contact the undersigned with any questions.

The Commissioner is hereby authorized to charge any needed fees to Deposit Account 50-1600.

Respectfully submitted,



Dated: March 22, 2010

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